The Clinical Usefulness of the Vaginal Smear

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SUMMARY

The chief value of the vaginal smear is as a simple, rapid means of accelerating the diagnosis of cancer in those cases in which the presenting symptoms or lesions are not sufficiently alarming to provoke immediate surgical investigation.

Carcinoma of the endocervix, carcinoma in situ, and carcinoma existing together with inflammatory and scarifying lesions are most likely to be discovered by the method. The very early ulcerative malignancy, before the fibrous proliferative reaction produces the classical raised edge and granular base, also has been detected on the smear taken just before the cautery was applied. The small nubbin without ulceration also yields malignant cells. These lesions almost always include the surface epithelium.

The positive smear has induced the immediate repetition of biopsy or curettage when the first sections have not confirmed a clinical suspicion. It can prevent temporizing when there is an easy explanation (such as estrogen administration or menopausal irregularity) for spotting and metrorrhagia. Examination of smears has corrected a number of false impressions caused by poor visualization.

The smear method is irreplaceable for the early diagnosis of recurrence after radiation. Salvage of the patient is rarely to be expected from such a discovery, but planning of palliative therapy is greatly aided.

THE rationale for cancer detection based upon vaginal smears depends upon the fact that epidermoid cancer sheds superficial cells in numbers far out of proportion to the size of the tumor. This tendency to exfoliate from the surface is not at all dependent upon the presence of ulceration; it is probably due to a biological property of cancer cells themselves. Cancer cells in tissue culture, for instance, have been observed to "break off" from the main clump and "metastasize" to other parts of the culture medium with greater ease than normal cells.

In essence the discovery of Papanicolaou and Traut was the demonstration of the frequency with which such cells appear, making possible their detection in a very small aliquot of the total vaginal exudate. The other thing these investigators demonstrated was that many malignant cells in isolated spread are sufficiently distinctive to make possible a strong presumption or certainty of their nature. It was shown that a great deal might be learned and that benefits to patients might accrue because by this approach genital carcinoma might be discovered early, whereas formerly there was only the random biopsy applicable in obvious lesions to demonstrate their character. From the outset Papanicolaou and Traut have emphasized that the effectiveness of this method depended upon examination of the smear by an experienced observer and substantiation by biopsy methods.

There are several reasons for this somewhat surprising reliability of certain diagnostic hallmarks in isolated malignant cells. One is that the very severe shrinking and wrinkling caused by suspension of tissue in a fixative is avoided. On smears the cells are spread out and flattened and frequently cover a greater area than they do even in situ. This can be easily demonstrated by examining fresh teased preparations in saline. The greater detail that can be seen is startling—not quite as much as is seen in dry smears of sternal marrow, for instance, but much more than can be seen even after fixation in solutions especially designed to minimize shrinkage, such as Zenker's. As a result, irregularity of nuclear outline is much more dependable as a criterion of malignancy in smears than in sections. Another unexpected advantage of smear staining is the very remarkable constancy of hematoxylin uptake by the nuclei. The variability of hematoxylin staining in sections seems to be partly due to the fact that when a large number of cells are crowded together, especially if the nuclei are closely approximated, the excess hematoxylin is mechanically hindered from diffusing out into the acid differentiating solution. The author has found it entirely unnecessary to control differentiation visually, as is done with section staining. The result of this constancy of staining is that the appearance of hyperchromatism is a much more valuable characteristic of isolated malignant cells than it is in sections.

By repeatedly looking at corresponding smears and sections, it eventually becomes easy to envision how cells in the one would look in the other. After two years of studying comparative material, the author is convinced of the value of having a smear as an aid in making a diagnosis if section examination is equivocal. This is not meant to violate the very proper practice of employing the biopsy as the yardstick whereby the reliability of the smear is measured. Nor does it mean that the biopsy need not determine the diagnosis. That the smear is not

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a substitute for biopsy has been emphasized by all observers, and it is to be hoped there is no more misunderstanding on that score. However, it is true that, as the examiner gains experience and confidence, there are some cells which are so distinctive and familiar to him that no number of negative biopsies would shake his belief in the presence of cancer. Learning about such cells is a subjective and individual matter and depends upon how much material has been examined. There is another large group of cells which are not diagnostic but which are derived from cancer 99 per cent of the time. Therefore, if these cells appear, the patient is suspected of cancer and should be followed for a very long time if the first diagnostic procedures do not demonstrate it. In this respect the vaginal smear method is different from most laboratory procedures; rapport should exist between the clinician and cytologist. This does not mean that the cytologist requires the clinical information. On the contrary, it has been found to be better that the cytologist know nothing about the patient until the cells have been evaluated; otherwise subjective errors will creep in. In the past, advocates of the method have had to use only the material which demonstrated the *reliability* of the diagnosis. They have had to refrain from demonstrating the additional group of cases in which the test is a more *sensitive* but only a *presumptive* indication of malignancy. It can be said that there are diagnostic smears and there are suspicious smears, and as experience is gained the former category enlarges and the latter increases in usefulness.

There are several situations in which the vaginal smear has an outstanding and special application. The first has already been suggested when equivocal biopsies were referred to. Those gynecologists who observe many patients with cancer are regrettably familiar with the small cervical lesion or even the larger one without well defined edges for which the biopsy report is an admirable piece of literature but without a title. Added to this is the lesion which looks like cancer but which upon biopsy is not shown to be cancer. It is instructive to consider that a smear is a sampling of the entire surface of the lesion and the biopsy section is a radial plane, ten micras thick, through the lesion. A positive smear does not wholly contradict a negative biopsy. It simply indicates the need for another biopsy.

CASE REPORTS

CASE NO. 1: A 55-year-old woman without gynecological symptoms had a circular reddened area about the cervical os, which was considered to be simple erosion. The smear showed innumerable malignant cells of the squamous type. The biopsy showed no epithelium except for a few rete pegs indistinguishable from normal downward extensions. (One hestitates to say this because anyone but a pathologist is apt to laugh at it, but it is quite possible to wipe the carcinoma right off the surface of a biopsy specimen.) Further biopsy material demonstrated carcinoma, and a section of the endocervix showed where most of the carcinoma was. This was an in situ carcinoma although the glands were penetrated. It is rather characteristic of in situ carcinoma to spread on the surface lining over a large area. There may be no ulceration or induration.

CASE NO. 2: A 53-year-old visitor at the anti-cancer clinic had no symptoms and the cervix looked perfectly normal. The rest of the pelvic examination was negative except for a mild atrophic vaginitis. The smears showed almost nothing other than carcinoma cells, even though they were taken from material in the posterior fornix. Section of the cervix showed that the carcinoma was lining the canal. The thin layer of cancer could be associated with no induration. A considerable number of smears were taken, to be used for teaching purposes, and they showed literally thousands of malignant cells.

The point may be made that the two cases reported are of the kind in which cancer is the least likely to be suspected on the basis of either presenting symptoms or pelvic examination; but the lesion sheds copious cells, and it is in such cases the chance of cure is best.

CASE NO. 3: A 52-year-old woman, one year past the menopause, complained of slight mucoid discharge for the previous five months. Pelvic examination disclosed a 1 cm. smooth translucent polyp protruding from the os and it was thought that this was the source of the discharge. Several small fibromyomata were also palpated. Vaginal smears showed striking clusters of cells with nuclear predominance, crowding irregularity, and hyperchromatism. Curettage revealed adenoacanthoma in the uterine cavity. After intracavitary radium treatment, the panhysterectomy specimen showed no remnant of carcinoma.

CASE NO. 4: A 32-year-old woman had had a supracervical hysterectomy and right salpingo-oophorectomy because of fibromyomata and endometrial cysts. Subsequently, an examination showed what was described as a "clean erosion" on the cervix. A smear was taken before cauterization and abundant malignant cells were found. Biopsy showed an early non-invading carcinoma.

The greatest value of the vaginal smear has been the acceleration of the diagnosis of cancer in women whose presenting symptoms or lesions were not sufficiently alarming to provoke surgical diagnostic measures. Without doubt, in most cases the diagnosis would have been made eventually, but many months have been saved, and not only by pathognomonic cells on the smears, but also by suspicious and even atypical cells. It is not the function of the vaginal smear to save the trouble of biopsy or curettage. On the contrary, it increases the frequency of these procedures.

The preparation of the vaginal smear is extremely simple and takes about 15 seconds. If a lesion is present on the cervix it should be scraped; if not, material from the posterior fornix or on the lower blade of the speculum is used. The smear need not be uniformly thin—a thickness just short of complete opacity is a good rule. The slides should then be placed immediately in an equal mixture of 95 per cent alcohol and ether before there is any drying. If there is no ether handy, 95 per cent alcohol is almost as good. After fixation for an hour, the slide may be allowed to dry and it retains its stainability for weeks. It is not necessary to transport the slides in fixative to the laboratory, and the author has found no advantage in

coating them with glycerine as has been advocated by others.

The method should not be considered as a screening test to "rule out cancer." In the author's series, approximately 4 per cent of proved cases have been missed on the smear. It is true that some of these smears were technically faulty, having been too scanty, or taken where bleeding was brisk so that nothing but blood was present on the smear. Nevertheless, "Rule out carcinoma" is a very unsuitable inscription on the request sheet.

CASE REPORT

CASE NO. 5: A 32-year-old woman complained of tenderness in the right lower quadrant. On pelvic examination a small amount of white discharge was seen in the external os. Smears from the posterior fornix showed many malignant cells, and upon reexamination a reddened granular area on the posterior lip was noted. It proved malignant on biopsy.

In most of the similar cases of poor visualization in which reexamination was instigated by positive smears, there were lesions on the posterior lip. It has been difficult to assess the "provocative" value of the vaginal smear in the presence of banal appearing lesions of the cervix because the description of the lesion on the second examination, after the positive smear report was given, has frequently been much more suggestive than the description given after the first examination.

At present, patients are not treated for cancer unless the biopsy warrants it. There is no need to compromise with this principle in the diagnosis of uterine cancer, although it may occasionally be justified in cancer of the lung when the tumor is located beyond the view through the bronchoscope.

A specialized application of the vaginal smear diagnosis is the detection of recurrence after radiation. This is usually only of prognostic value but may frequently aid in planning palliative therapy.

Case detection at anti-cancer clinics in the eastern United States has been low—about one case in 500 visitors. Data from similar clinics for which examinations are done by the University of California Cytological Laboratory have not yet been analyzed. It has been stated that an undue amount of time and labor is required for the yield, but the technicians at the Cytological Laboratory have not found such material particularly burdensome. A well trained, experienced technician can screen a slide without unusual cell components in five minutes and when the anti-cancer slides are received in small groups and distributed among several technicians there is no great effort required. No increase of staining time is needed at all; the slides are stained in batches and it takes no longer to stain 20 than to stain one.

Technicians can be trained in about four months to recognize suspicious cells. Their task is to mark them for evaluation by the cytologist. Because of the time required, it is not practicable for a pathologist to do his own screening.